REMARKS

STATUS OF THE CLAIMS

Claims 17-28 were examined in the final Office Action dated November 10, 2005. Applicants submitted an Amendment under 37 C.F.R. § 1.116 on January 9, 2006. Applicants received an Advisory Action dated January 31, 2006. The Advisory Action maintained all rejections of the claims, did not enter any of the amendments filed in the response to the Final Office Action, and objected to the amendments as not being in compliance with 37 C.F.R. 1.121 due to duplicate numbering.

Claim 17 has been amended to recite a capsular oligosaccharide. Claim 20 has been amended to recite a NmC oligosaccharide containing 12 to about 22 repeating units. Support for these amendments is found throughout the specification and thus Applicants assert that no new matter has been added.

Applicants have corrected the claim numbering for the withdrawn method claim, which was misnumbered as claim 25 in the response to the Final Office Action.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the cancelled or unamended claims.

Upon entry of the amendments, claims 17 to 28 are pending in the present application. Claim 29 is presently withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a) – 3 References

Claims 17-23 and 25-27 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) and van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996).

The applicants respectfully traverse. In order to establish a *prima facie* case of obviousness, three criteria must be met: (1) the cited references must teach or suggest all elements of the claimed invention, (2) there must be a teaching or suggestion to modify or combine the references, and (3) there must be a reasonable expectation of success.

1. *No Motivation to Combine*

Since there is no motivation to combine, there is no *prima facie* case of obviousness. As discussed in the previous responses, van der Voort *et al.* do not mention oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier and Constantino *et al.* do not mention proteoliposomic vesicles from serogroup B of *N. meningitidis* (NmB). There can be no teaching or suggestion to combine one with the other where they do not mention anything in relation to the other. To remedy this lack of motivation, the Examiner has asserted that Paradiso *et al.* provides the motivation to combine, specifically citing to the following paragraph bridging pages 272 and 273:

> A significant portion of the morbidity from meningococcus is caused by group B. Unfortunately, the capsule from group B is not very immunogenic in people because of the similarity to saccharide structures on human cells. For this reason, and because of the potential for anti-group B antibody to cross-react with brain tissue, alternative approaches have been sought. Most of the work has been done on outer membrane vesicles prepared from cells of virulent group B strains [10]. It seems likely that in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates. Since these vesicle preparations contain an array of proteins and lipids, the combinations ***will create a new set of formulation challenges*** not unlike those encountered in mixing conjugate vaccines with DTP. [emphasis added]

In order to provide a motivation to combine, a reference must suggest the ***desirability*** of making the combination. Paradiso *et al.* do not cite to a reason that would motivate one of skill in the art to combine the references. Rather, Paradiso *et al.* only suggest that in the future there may be some uncited reason making it desirable to combine outer membrane-vesicle based group B vaccines with group C conjugates. Further, in the very next sentence, Paradiso *et al.* state that there ***will*** be

challenges to formulation of such a combination. Therefore, Paradiso *et al.* teach that there is no motivation today, but at best there may be a motivation in the future, and that those of skill in the art will face difficulties at such future time in making the combination.

2. *No Reasonable Expectation of Success*

Even if Paradiso *et al.* could be read as teaching or suggesting some reason that it would be desirable to combine the teachings of Constantino *et al.* and van der Voort *et al.*, one of skill in the art would not have a reasonable expectation of success of this combination and therefore there would still be no *prima facie* case for obviousness.

The Examiner has used impermissible hindsight to find that there was a reasonable expectation of success by those of skill in the art at the time of the invention. A reasonable expectation of success exists only when a person of ordinary skill has a reasonable expectation that a beneficial result ***will be achieved.*** *In re Merck & Co., Inc.,* 800 F.2d 1091 (Fed. Cir. 1986). The test is not whether the experimentation required to achieve success is routine, but rather whether one of ordinary skill would reasonably expect such experimentation to be ultimately successful. Applicants' success in making the claimed invention cannot be used as evidence that the success would have been reasonably expected. *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320 (Fed. Cir. 2000).

Paradiso *et al.* itself, as well as other references in the art at the time of the invention, taught one of ordinary skill in the art that certain combinations of the components of certain individual vaccines will never be effective, regardless of how many attempts are made to optimize the formulation. Given this inherent unpredictability of combination vaccines, one of skill in the art could not have had a reasonable expectation of success for any particular combination vaccine until it was actually shown to work, such as we have done for the instant invention.

As noted above, Paradiso *et al.* state that there ***will*** be challenges when combining group B vaccines with group C conjugates, not just that there *might* be difficulties. Thus, the very reference that the Examiner has asserted to provide a motivation to combine states that there will be

challenges that must be overcome, indicating that one of skill in the art would not have a reasonable expectation of success. Furthermore, Paradiso *et al.* provide data in Table 5 on page 273 comparing a multivalent vaccine with separate application of the individual vaccine components. As discussed by Paradiso *et al.* on page 273, certain of the components produced a weaker immune response in the multivalent vaccine and certain components produced a stronger immune response in the multivalent vaccine, thus demonstrating how individual components can behave in an unpredictable fashion when combined.

A 1996 Report on "New Vaccines, Especially New Combined Vaccines" (attached to IDS) elaborates on the multiple problems which make it difficult to predict whether a particular combination vaccine will be effective. The report emphatically warns those of skill that many combination vaccines will not work, stating: "It has been found that when two existing vaccines are simply mixed, one or both ***usually*** lose their potency." (p. 694, col. 1, bridging paragraph). Referring to the combination of Hib with various other vaccines as an example, the report concludes that combining two existing vaccines is ***not simple*** and often gives ***very unpredictable*** results. The report further warns those of skill about the difficulties in developing combination vaccines with sufficiently low levels of reactogenicity, stating: "one can also envisage an ... increase in reactogenicity of one or several components... If increased reactogenicity is observed, it will be ***very difficult*** to identify the responsible component in the combined vaccine."

Corbel (attached to IDS) is a further example of how the art at the time of invention taught that the success of combination vaccines was unpredictable. Corbel is devoted to a discussion of the need for appropriate quality control procedures to screen for effective and safe combination vaccines. If the success of combination vaccines was predictable, this type of article would be completely unnecessary. Corbel's position on the unpredictability of combination vaccines is made explicit in the abstract, which states: "The requirements for new vaccine combinations need to be considered carefully and should *not* be made solely based on assumptions based on the properties of individual components."

Thus, given the teachings in the art, one of skill could not have had a reasonable expectation that the claimed NmC/NmB combination vaccine would be successful. At best, one of skill could only have a hope or wish that extensive experimentation would produce a successful combination vaccine. While the 1996 Report offers some future directions for research designed to facilitate the development of combination vaccines (p.695-696) and Corbel acknowledges that some of the problems may be amenable to management (p.360), both references fail to offer any specific solutions or strategies upon which one of skill might base a reasonable expectation of success for any particular combination vaccine.

3. *References Teach Away*

Even if a *prima facie* case of obviousness has been established, a *prima facie* case may be rebutted where there is evidence of teaching away. Teaching away may come in the form of a reference criticizing, discrediting or otherwise discouraging the solution claimed.

Paradiso *et al.* clearly teach away from combining the teachings of Constantino *et al.* and van der Voort *et al.* in three ways. As discussed above, Paradiso *et al.* talk of a future desirability which implies that there is no reason at present to make the combination. Paradiso *et al.* also talk of challenges that must be overcome before such combination would actually work. Paradiso *et al.* also show that the results of combining vaccines are unpredictable, which suggests that such combination may never work. All three of these teachings would discourage one of skill in the art from attempting the presently claimed invention.

4. *References Fail to Provide All Elements of Claims 20 and 26-28*

In addition to the above, the three cited references fail to provide all elements of claims 20 and 26-28 and therefore fail to establish a *prima facie* case of obviousness. Amended Claim 20 includes the limitation that the "NmC oligosaccharide contains 12 to about 22 repeating units" and claim 26 (and therefore dependent claims 27-28) includes the limitation that the first antigen "contains from 12 to 22 repeating units from the NmC capsular polysaccharide ..." van der Voort *et al.* do not mention oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a

carrier at all and Constantino *et al.* do not mention oligosaccharides from serogroup C *N. meningitidis* (NmC) conjugated to a carrier where the oligosaccharides contain 12 to 22 repeating units. As noted by the Examiner, Constantino *et al.* mention oligosaccharides having a polymerization degree (DP) of up to 10. Paradiso *et al.* fail to remedy this lack as it only cites to Constantino *et al.* Thus, the three cited references fail to teach or suggest all elements of claims 20 and 26-28.

Applicants therefore respectfully request that the Examiner withdraw the 35 U.S.C. 103(a) rejection of claims 17-23 and 25-27 as there is no motivation to combine the references and no reasonable expectation of success for such combination, and even if there were both, Paradiso *et al.* teach away from the claimed invention by discouraging one of skill in the art from attempting the combination. In addition, the references fail to teach an element of claims 20 and 26-28.

REJECTION OF CLAIMS 24 and 28 UNDER 35 U.S.C. § 103(a) – 4 References

Claims 24 and 28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) and van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996) as applied to claim 17 or 26 above, and in further view of Granoff (US 6,413,520).

Applicants respectfully traverse. Granoff is not available under 102(e) as prior art. MPEP § 2136.03(II)(C)(1) clearly indicates that a U.S. Patent which claims priority to an international application filed before November 29, 2000 has a critical reference date as of the earlier of the date of completion of 35 U.S.C. 371(c)(1), (2) and (4) or the filing date of the later-filed application that claimed the benefit of the international application. Granoff indicates on its face that the date of completion of 35 U.S.C. 371(c)(1), (2) and (4) was Dec. 16, 1999 (See (86) on the cover page). Since the international application PCT/US98/13080 was filed before November 29, 2000, the critical date for Granoff is Dec. 16, 1999. Since the priority date of the present application is well before Dec. 16, 1999, Granoff does not qualify as 102(e) prior art. Therefore the

citable references fail to teach "a carrier comprising polylactic acids or polyglycolic acids" as claimed under 24 and 28. Therefore a *prima facie* case of obviousness has not been established.

In addition as discussed above, the first three references fail to render the claims obvious as there is no motivation to combine the references, there is no reasonable expectation of success for such combination, and even if there were both, Paradiso *et al.* teach away from the claimed invention by discouraging one of skill in the art from attempting the combination. The three citable references also fail to teach another element of claim 28.

Applicants therefore respectfully request that the Examiner withdraw the 35 U.S.C. 103(a) rejection of claims 24 and 28 for at least the above reasons.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In addition, please direct all further communications in this application to:

Alisa A. Harbin
Chiron Corporation
Intellectual Property – R440
P.O. Box 8097
Emeryville, CA 94662-8097
Tel: (510) 923-2708
Fax: (510) 655-3542

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **223002100100**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 9, 2006

Respectfully submitted,

By _____
Otis Littlefield
Registration No.: 48,751
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
(415) 268-6846